REMARKS

Applicant's counsel thanks the Examiner for the careful consideration given the application. Claim 26 has been amended, as requested by the Examiner at page 6 of the Office action, to highlight the characterising feature of the method according to the invention. Basis for the amendment can be found in the Application at page 4, line 30-34. The feature regarding the integrator has been removed as it was stated by the Examiner that this was superfluous. Basis for a method to prepare an integrator can be found at page 4, line 30-31.

Basis for the addition of the number of water molecules present can be found in the Application at page 4, line 16-18

Basis for the addition of MHA can be found in the Application at page 4, line 32.

Claim 28 has been amended to better describe the method. The basis can be found on page 4, line 3-16.

Basis for the amendment to claim 36 can be found at page 8 lines 19-21.

Claim 39 is new and finds basis at page 8, lines 19-24.

ARGUMENTS

The Examiner rejects claims 26-38 under §103 by a combination of features taught in Ashmead 1 and Ciribolla. The features cited by the Examiner featured in Ashmead 1 do not relate to the reaction as claimed in the current Application and therefore would not be considered by the person skilled in the art as probative or indicative. This is because the method claimed in the current application starts with methionine hydroxyl analogue (MHA) and Ashmead 1 does not. Ashmead 1 discloses only a method starting with natural amino acids and $CaO/Ca(OH)_2$. (ref. col.6, line 34-37) These are **different reactants.**

The Examiner cites methionine as one of the amino acids present in Ashmead 1 at col.6, lines 15-20. The name is confusingly similar to that of MHA, but the person skilled in the art would recognise that the difference chemically between methionine and methionine hydroxyl analogue (MHA) is great. MHA is an **α-hydroxyde acid**, while methionine is an **α-amino acid**. The difference in the α-amino and α-hydroxy group leads to different and not comparable chemical properties due to different basicity and electron inductive effect. The difference is so chemically pronounced that MHA is not derivable from methionine. Thus the person skilled in the art would not treat MHA as derivative of methionine and would not consider the teaching of Ashmead 1 pertinent because both reactant and product are notably different.

Please find enclosed copies of the two entries within the Merck Index, thirteenth edition, as proof of the different chemical nature of the methionine and MHA (entry 6004 and entry 6005 respectively). Their CAS registry number - the number within the square brackets in the entries' description - are different and this illustrates how different they are chemically.

The person skilled in the art would consider Ashmead 1 also not pertinent because it describes a two step process, where it is essential to be free of interfering ions for the complexing of the metal ion to the α-amino group (ref. col.4, line 39-45):

"*the introduction of mineral acid salts into solution, such as copper sulfate, resulted in the creation of copper ions which compete with the hydrogen ion for the lone pair of electrons on the NH2 group. Unfortunately, the equilibrium favors the majority of the amino groups remaining protonated. Thus, in order to efficiently chelate metal ions from certain soluble salts, it becomes desirable to render the interfering ions inactive or use soluble metal salts with non-interfering ions, such as oxides or hydroxides*"

By ridding the α-amino group of protons according to the two-step reaction, the metal can be complexed to the α-amino group of methionine. The person skilled in the art would thus ignore any teaching of Ashmead 1 because it describes an **unnecessarily more complicated reaction**, as the amino group in MHA does not exist and thus it cannot be freed in a two-step reaction.

The reactants are different, the reaction is different and the products are also different. It is clear from the foregoing that Ashmead 1 does not provide any teaching or suggestion for the use of MHA in accordance with the present invention.

The Examiner is correct in noting that Ciribolla teaches a direct reaction between MHA with a metal carbonate. Even though the abstract asserts that this reaction is free of undesirable by-products, the teaching of Ciribolla clearly **shows this is not the case**:

> *The mixer is turned on and the methionine hydroxy analogue is added slowly so as to avoid the undesirable effects of a strong evolution of CO_2 and overheating of the mixture* (Ref. Col. 3, line 32-35 of Ciribolla).

and

> *During the entire reaction, the methionine/metal carbonate stoichiometric ratio is less than the theoretical ratio, approaching the theoretical value asymptotically at the end of the reaction.* (Ref. Col. 3, line 41-44 of Ciribolla).

The advantage of the present invention is that **both these undesirable side effects are overcome** by the reactions according to the present invention. There is no suggestion or teaching for the person skilled in the art in Ciribolla that this could be achieved by using direct reactions according to the present invention. Thus it is clear that the person skilled in the art is not motivated and nor could he find the teaching of the present invention if he were to combine these documents.

Even if the person skilled in the art would combine the Ashmead 1 and Ciribolla documents, a supposition the Applicant does not agree with and contests, he would not be able to perform the reaction according to the present invention. This is because the combination of Ashmead 1 and Ciribolla would give a reaction between an amino acid and a metal carbonate. The difference in pK_1 between methionine and MHA, as described above, would suggest the person skilled in the art to use methionine and not MHA to form a proteinate chelate. The other reactant would have to derive from the other document to be combined, therefore Ciribolla, and the only reactant which could possibly give metals featured therein is a

metal carbonate. Thus the outcome would be a reaction between an amino acid and a metal carbonate and not the reaction according to the present invention (metal oxide + MHA).

Ashmead 2, as explained by the Examiner at page 8 of the Office action, is only related to the teaching of administering metal proteinates in biological tissues. It is thus not related to the method of preparation thereof. Hence it is clear that the claims for the preparation of metal chelates according to the present invention is not rendered obvious by any teaching or suggestion of Ashmead 2, alone or in combination with the other documents, Ashmead 1 and Ciribolla, as explained above.

For all the reasons above, it is clear that the claims as now presented are not taught or suggested by the three applied references, taken separately or together. According, it is submitted that the present claims are now in condition for allowance, which is respectfully requested.

If there are any fees required by this communication that are not covered by an enclosed check, please charge any such fees to our Deposit Account 16-0820, Order No. 37891.

Respectfully submitted,
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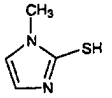
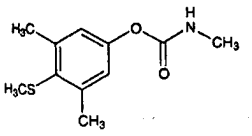
...vents. LD_{50} in adult male, female rats (mg/kg): 31, 32 orally (Gaines, Linder).
USE: Insecticide, acaricide.

6000. Methimazole. [60-56-0] 1,3-Dihydro-1-methyl-2*H*-imidazole-2-thione; 1-methylimidazole-2-thiol; 1-methyl-2-mercaptoimidazole; mercazolyl; thiamazole; Basolan; Danantitox; Favistan, Frentirox; Mercazole; Metazolo; Tapazole; Thazol; Thycapsol; Strumazol. $C_4H_6N_2S$; mol wt 114.17. C 42.08%, H 5.30%, N 24.54%, S 28.09%. Prepd by treating aminoacetaldehyde diethyl acetal with methyl isothiocyanate: Riehl, Marckwald, *Ber.* **22,** 1354 (1889); from thiocyanic acid and *N*-substituted amino acetals: Jones *et al., J. Am. Chem. Soc.* **71,** 4000 (1949). Metabolism: D. S. Sitar, D. P. Thornhill, *J. Pharmacol. Exp. Ther.* **184,** 432 (1973). Comprehensive description: H. Y. Aboul-Enein, A. A. Al-Badr, *Anal. Profiles Drug Subs.* **8,** 351-370 (1979). Review of pharmacology and clinical experience: D. S. Cooper, *N. Engl. J. Med.* **311,** 1353-1362 (1984).



Leaflets from alc, mp 146-148°. bp 280° (some decompn). ν max (0.1*N* H_2SO_4): 211, 251.5 nm ($E^{1\%}_{1cm}$ 593, 1528). Freely sol in water. Sol in alcohol, chloroform. Sparingly sol in ether, petr ether, benzene.
Methiodide. Jomezol.
USE: In cyanide-free silver electroplating.
THERAP CAT: Antihyperthyroid.

6001. Methiocarb. [2032-65-7] 3,5-Dimethyl-4-(methylthio)phenol methylcarbamate; methylcarbamic acid 4-(methylthio)-3,5-xylyl ester; 4-(methylthio)-3,5-xylyl methylcarbamate; 4-methylthio-3,5-dimethylphenyl *N*-methylcarbamate; mercaptodimethur; metmercapturon; Bayer 37344; H-321; Draza; Mesurol. $C_{11}H_{15}NO_2S$; mol wt 225.31. C 58.64%, H 6.71%, N 6.22%, O 14.20%, S 14.23%. Prepn: E. Schegk *et al.*, GB 912895; *eidem*, US **3313684** (1962, 1967 both to Bayer); E. E. Gilbert, J. A. Otto, US **3358012** (1967 to Allied). Molluscicidal activity: H. H. Crowell, *J. Econ. Entomol.* **60,** 1048 (1967). Bird repellent properties: E.W. Schafer, R. B. Brunton, *J. Wildl. Manage.* **35,** 569 (1971). Toxicity study: T. B. Gaines, *Toxicol. Appl. Pharmacol.* **14,** 515 (1969).

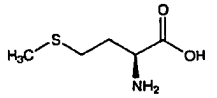


White crystalline powder, mp 121.5°. Insol in water. Sol in organic solvents. Unstable in alk media. LD_{50} in male, female rats (mg/kg): 70, 60 orally (Gaines).
USE: Insecticide; molluscicide; bird repellent.

6002. Methiodal Sodium. [126-31-8] Iodomethanesulfonic acid sodium salt; sodium iodomethanesulfonate; Skiodan; Abrodil; Radiographol; Segosin; Diagnorenol. CH_2INaO_3S; mol wt 243.98. C 4.92%, H 0.83%, I 52.01%, Na 9.42%, O 19.67%, S 13.14%. CH_2ISO_3Na. Prepd by the action of sodium sulfite on methylene iodide at 70° in water-alcohol soln: Ossenbeck *et al.*, US **1842626** (1932 to Winthrop); from iodoform + sodium sulfite: Allardt, US **1867793** (1932 to Schering-Kahlbaum AG).
Crystals. Slightly saline taste followed by sweetish aftertaste. Freely sol in water (70 g/100 ml); slightly sol in alcohol (2.5 g/100 ml), benzene, ether, acetone.
THERAP CAT: Diagnostic aid (radiopaque medium—urographic).

6003. Methionic Acid. [503-40-2] Methanedisulfonic acid. $CH_4O_6S_2$; mol wt 176.17. C 6.82%, H 2.29%, O 54.49%, S 36.40%. $CH_2(SO_3H)_2$. Prepn from methane + sulfur trioxide: Snyder, Grosse, US **2493038** (1950 to Houdry Process); by H_2SO_4 oxidation of acetic acid: Schwab, Neuwirth, *Ber.* **90,** 567 (1957); from $MeSO_3H$ + SO_3: Crowder, Gilbert, US **2842589** (1958 to Allied Chem.). Prepn of aluminum salt: Christian, Jenkins, *J. Am. Pharm. Assoc.* **39,** 633 (1950); US **2504107** (1950 to Purdue Res. Found.).
Crystals, mp 96-100°.
Aluminum salt. $C_3H_6Al_2O_{18}S_6$. Crystals from water + alcohol. Hygroscopic. Soly in water at 27°: 69 w/v. pH of 5% aq soln = 3.5.
USE: Antiperspirant.
THERAP CAT: Aluminum salt as topical astringent.

6004. Methionine. [63-68-3] L-Methionine; Met; M; 2-amino-4-(methylthio)butyric acid; α-amino-γ-methylmercaptobutyric acid; (*S*)-2-amino-4-(methylthio)butanoic acid; γ-methylthio-α-aminobutyric acid; Acimethin. $C_5H_{11}NO_2S$; mol wt 149.21. C 40.25%, H 7.43%, N 9.39%, O 21.44%, S 21.49%. Essential amino acid for human development. Universal translation start signal although usually missing from mature protein. Isoln from casein: J. H. Mueller, *Proc. Soc. Exp. Biol. Med.* **19,** 161 (1922). Early chemistry and biochemistry: *Amino Acids and Proteins,* D. M. Greenberg, Ed. (Charles C. Thomas, Springfield, IL, 1951) 950 pp., *passim*; J. P. Greenstein, M. Winitz, *Chemistry of the Amino Acids* vols. 1-3 (John Wiley and Sons, Inc., New York, 1961) pp. 2125-2155, *passim.* Determn and distribution in non-protein fractions: J. Giovanelli, S. H. Mudd, *J. Biochem. Biophys. Methods* **11,** 1 (1985). GC-MS determn in biological fluids: S. P. Stabler *et al., Anal. Biochem.* **162,** 185 (1987). Evaluation as tracer in cancer imaging in mice: R. Kubota, *J. Nucl. Med.* **36,** 484 (1995). Clinical evaluation in acetaminophen overdose: A. N. Hamlyn *et al., J. Int. Med. Res.* **9,** 226 (1981). Clinical use as radiolabel in hyperparathyroidism: P. Hellman *et al., Surgery* **116,** 974 (1994). Review of metabolism and clinical significance in man: L. D. Fleisher, G. E. Gaull, *Clin. Endocrinol. Metab.* **3,** 37-55 (1974); and in carcinogenesis: T. L. Gatton-Umphress, *Hosp. Pract.* **28,** 83-90 (1993). Review of toxicity: N. J. Benevenga, *J. Agric. Food. Chem.* **22,** 2-9 (1974). Review of biosynthesis: I. G. Old *et al., Prog. Biophys. Mol. Biol.* **56,** 145-185 (1991). Review as translation start signal: T. Meinnel *et al., Biochimie* **75,** 1061-1075 (1993).



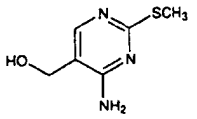
Minute hexagonal plates from dil alc, mp 280-282° (dec, sealed capillary). $[\alpha]_D^{25}$ −8.11° (c = 0.8). $[\alpha]_D^{20}$ +23.40° (c = 5.0 in 3*N* HCl). Sol in water, but the crystals are somewhat water-repellent at first. Sol in warm, dil alcohol. Insol in abs alcohol, ether, petr ether, benzene, acetone.
D-Form. [348-67-4] Converted by deamination, followed by transamination with resultant inversion to the L-form. Comparative study with L-form of metabolism in plants: M. Pokorny *et al., Phytochemistry* **9,** 2175 (1970). Evaluation in parenteral nutrition: K J. Printen *et al., Am. J. Clin. Nutr.* **32,** 1200 (1979). *Review:* L. D. Stegink, D-Amino Acids in *Clin. Nutr. Update: Amino Acids,* H. L. Greene *et al.,* Eds. (American Medical Association, Chicago, IL, 1977) pp 198-206. $[\alpha]_D^{25}$ +8.12° (c = 0.8). $[\alpha]_D^{25}$ −21.18° (c = 0.8 in 0.2*N* HCl).
DL-Form. [59-51-8] Racemethionine; Banthionine; Dyprin; Lobamine; Metione; Pedameth; Urimeth. Platelets from alc, mp 281° (decompn). d 1.340. pK_1 2.28; pK_2 9.21. pH of 1% aq soln 5.6-6.1. R_f value 0.77. Soly in water (g/l) at 0°: 18.18; at 25°: 33.81; at 50°: 60.70; at 75°: 105.2; at 100°: 176.0. Sol in dil acids, alkalies. Very slightly sol in 95% alcohol. Insol in ether.
THERAP CAT: Hepatoprotectant; antidote (acetaminophen poisoning); urinary acidifier.
THERAP CAT (VET): Nutritional supplement; urinary acidifier.

6005. Methionine Hydroxy Analog. [583-91-5] 2-Hydroxy-4-(methylthio)-butanoic acid; 2-hydroxy-4-(methylthio)-butyric acid; 2-hydroxy-4-(methylmercapto)butyric acid; Alimet. $C_5H_{10}O_3S$; mol wt 150.20. C 39.98%, H 6.71%, O 31.96%, S 21.35%. $CH_3SCH_2CH_2CH(OH)COOH$. Prepn (not claimed) and use as poultry feed additive: E. S. Blake, R. J. Wineman, **US 2745745** (1956 to Monsanto). HPLC determn in feeds: A. Baudichau *et al., J. Sci. Food Agr.* **38,** 1 (1987). Use as a feed additive for livestock: A. Papas *et al., J. Nutr.* **104,** 653 (1974); A. K. Clark, A. H. Rakes, *J. Dairy Sci.* **65,** 1493 (1982); D. H. Reifsnyder *et al., J. Nutr.* **114,** 1705 (1984). Efficacy of calcium salt vs free acid: K. P. Boebel, D. H. Baker, *Poultry Sci.* **61,** 1167 (1982).

Calcium salt. MHA. $C_{10}H_{18}CaO_6S_2$; mol wt 338.46.

USE: Dietary supplement in livestock.

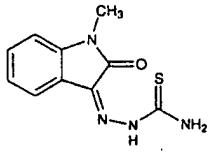
6006. Methioprim. [588-36-3] 4-Amino-2-methylthio-5-pyrimidinemethanol; 4-amino-2-methylmercapto-5-pyrimidinemethanol; 4-amino-5-hydroxymethyl-2-methylthiopyrimidine. $C_6H_9N_3OS$; mol wt 171.22. C 42.09%, H 5.30%, N 24.54%, O 9.34%, S 18.73%. Synthesis starting with ethyl ethoxyethylenecyanoacetate: Ulbricht, Price, *J. Org. Chem.* **21,** 567 (1956).



Needle-like prisms from benzene, mp 126-127°.

USE: Tumor antagonist in mice.

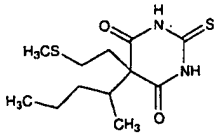
6007. Methisazone. [1910-68-5] 2-(1,2-Dihydro-1-methyl-2-oxo-3*H*-indol-3-ylidene)hydrazinecarbothioamide; 1-methylindole-2,3-dione 3-thiosemicarbazone; *N*-methylisatin 3-thiosemicarbazone; BW-33-T-57; Marboran; Viruzona. $C_{10}H_{10}N_4OS$; mol wt 234.28. C 51.27%, H 4.30%, N 23.91%, O 6.83%, S 13.69%. Prepn: Bauer, Sadler, *Brit. J. Pharmacol.* **15,** 101 (1960); **GB 975357** (1964 to Wellcome Found.).



Crystals from butanol, mp 245°.

THERAP CAT: Antiviral.

6008. Methitural. [467-43-6] Dihydro-5-(1-methylbutyl)-5-[2-(methylthio)ethyl]-2-thioxo-4,6(1*H*,5*H*)-pyrimidinedione; 5-(1-methylbutyl)-5-[2-(methylthio)ethyl]-2-thiobarbituric acid; 5-(2-methylthioethyl)-5-(2-pentyl)-2-thiobarbituric acid. $C_{12}H_{20}N_2O_2S_2$; mol wt 288.43. C 49.97%, H 6.99%, N 9.71%, O 11.09%, S 22.23%. Prepn: Zima, Von Werder, **US 2802827** (1957 to E. Merck).

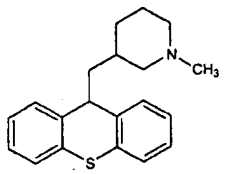


Sodium salt. [730-68-7] Methioturiate; AM-109; Sch-3132; Neraval; Thiogenal. $C_{12}H_{19}N_2NaO_2S_2$; mol wt 310.42. Very hygroscopic, yellow crystals. Slight odor of mercaptans. Freely sol in water. pH of a 10% aq soln ~9.5. Water solns are unstable as evidenced by a deepening of color and formation of a cloudy precipitate upon autoclaving and exposure to light. The addition of sodium carbonate has a stabilizing effect and prevents precipitation for about 24 hrs: Irwin *et al., J. Pharmacol. Exp. Ther.* **116,** 317 (1956).

Caution: May be habit forming: **21 CFR,** 329.1 and is a controlled substance (depressant): **21 CFR,** 1308.13.

THERAP CAT: Sedative, hypnotic.

6009. Methixene. [4969-02-2] 1-Methyl-3-(9*H*-thioxanthen-9-ylmethyl)piperidine; 9-(*N*-methyl-3-piperidylmethyl)-thioxanthene. $C_{20}H_{23}NS$; mol wt 309.48. C 77.62%, H 7.49%, N 4.53%, S 10.36%. Anticholinergic. Prepn: Caviezel *et al., Pharm. Acta Helv.* **33,** 447 (1958); J. Schmutz, **US 2905590** (1959 to Wander). Metabolism and toxicity study: H. Lehner *et al., Arzneimittel-Forsch.* **14,** 89 (1964). Crystal structure: S. S. C. Chu, *Acta Crystallogr.* **B28,** 3625 (1972). Spectrofluorimetric determn: F. Belal *et al., Anal. Chim. Acta* **255,** 103 (1991). Comprehensive description: E. M. Abdel-Moety *et al., Anal. Profiles Drug Subs. Excip.* **22,** 317-358 (1993).

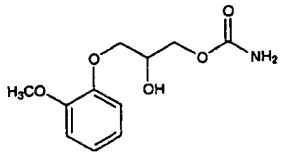


Slightly yellow viscous liquid, $bp_{0.07}$ 171-175°. Insol in water.

Hydrochloride monohydrate. [7081-40-5] Tremoquil; Methixart; Trest; Tremonil; Tremaril; Tremarit; Cholinfall; Methyloxan. $C_{20}H_{23}NS.HCl.H_2O$; mol wt 363.95. Flakes from ether, mp 215-217°. uv max (dil HCl): 268 nm (ε 10250). Sol in water, alcohol, chloroform. Insol in ether.

THERAP CAT: Antiparkinsonian.

6010. Methocarbamol. [532-03-6] 3-(2-Methoxyphenoxy)-1,2-propanediol 1-carbamate; 3-(*o*-methoxyphenoxy)-2-hydroxypropyl 1-carbamate; 2-hydroxy-3-(*o*-methoxyphenoxy)propyl 1-carbamate; guaiacol glyceryl ether carbamate; AHR-85; Neuraxin; Miolaxene; Lumirelax; Etroflex; Delaxin; Robamol; Traumacut; Tresortil; Relestrid; Robaxin. $C_{11}H_{15}NO_5$; mol wt 241.24. C 54.77%, H 6.27%, N 5.81%, O 33.16%. Prepn from 3-(*o*-methoxyphenoxy)-2-hydroxypropyl chlorocarbonate: Murphey, **US 2770649** (1956 to A. H. Robins). Comprehensive description: S. Alessi-Severini *et al., Anal. Profiles Drug Subs. Excip.* **23,** 371-399 (1994).



Crystals from benzene, mp 92-94°. uv max (water): 222, 271 nm ($E^{1\%}_{1cm}$ 298, 94). log P −0.06. Soly in water at 20°: 2.5 g/100 ml. Sol in alcohol, propylene glycol. Sparingly sol in chloroform. Practically insol in *n*-hexane.

THERAP CAT: Muscle relaxant (skeletal).

THERAP CAT (VET): Muscle relaxant (skeletal).

6011. Methohexital Sodium. [22151-68-4] 1-Methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl)-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione sodium salt; 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid sodium salt; α-*dl*-1-methyl-5-(1-methyl-2-pentynyl)-5-allylbarbituric acid sodium salt; α-*dl*-1-methyl-5-allyl-5-(1-methyl-2-pentynyl)barbituric acid sodium salt; methohexitone sodium; Brevital; Brevital Sodium; Brevimytal Sodium; Brietal Sodium. $C_{14}H_{17}N_2NaO_3$; mol wt 284.29.